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EXAMINER
TOUZEAU, [illegible]

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ART UNIT	PAPER NUMBER
1615	24

DATE MAILED: 12/29/92

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on ______ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ ______

Part II SUMMARY OF ACTION

1. ☒ Claims 1-12 are pending in the application.

   Of the above, claims ______ are withdrawn from consideration.

2. ☐ Claims ______ have been cancelled.
3. ☐ Claims ______ are allowed.
4. ☒ Claims 1-12 are rejected.
5. ☐ Claims ______ are objected to.
6. ☐ Claims ______ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on ______. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on ______ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on ______, has been ☐ approved. ☐ disapproved (see explanation).
12. ☒ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☒ been received ☐ not been received ☐ been filed in parent application, serial no. ______ ; filed on ______.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

PTOL-326 (Rev. 9-89)

EXAMINER'S ACTION

15. Claims 1, 7, 4 and 12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claims 1 and 12, the phrase "where appropriate" is indefinite because that point is not defined in clear and exact terms. The term "derivatives" in claims 1 and 12 is also indefinite as there is no absolute basis to determine what is a derivative and what is not. In claim 7, the term "derives from" is indefinite because it is not clear in what manner the F VIII:C activity is derived. The term "customary" in claim 10 is indefinite as what is customary in pharmaceutically compatible, stabilizing and/or buffering substances is not described in clear and exact language.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

16. Claims 1, 2, 3, 6, 8 and 12 are rejected under 35 U.S.C. § 102(a) as being anticipated by Meyers et al. (Meyers). Meyers discloses a large scale adaptation of a recently reported glycine

0.25 M and glycine at a concentration of about 0.28 M (column 8, lines 53-62). His product is to be used as a pharmaceutical as he discloses that the primary therapeutic use of Factor VIII (Factor VIII:C) has been its intravenous administration to hemophiliac patients to control bleeding (column 1, lines 32-33). Therefore, Applicant's invention was anticipated in the prior art by Kosow.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

18. Claims 1-12 are rejected under 35 U.S.C. § 103 as being unpatentable over Meyers et al. (Meyers) in view of Mathews and further in view of Rasmussen. Meyers, as discussed above, discloses the large-scale preparation of a highly purified solvent-detergent concentrate of Factor VIII:C. Although he does not teach a pharmaceutical containing a solution, he does teach that his concentrate is considered to be suitable for clinical

precipitation method for the production of Factor VIII:C concentrate. Said method includes adding aluminum hydroxide to a glycine buffer to reduce the level of protein contamination in the final preparation. Furthermore, the resultant product was virus-inactivated by the incorporation of the organic solvent and detergent (TNBP and T80) technique (abstract). At the industrial level, this method gave 185 IU of FVIII:C activity per liter of starting plasma, which the Examiner deems to be at least equivalent to Applicants' yield. The starting material for the preparation of the product was obtained from volunteer donors. The final product was a sterile filtered solution that was ultimately lyophilized for storage and considered to be suitable for clinical evaluation (abstract). Thus, one would immediately and at once envisage a solution with Factor VIII:C activity containing a basic amino acid such as glycine and a nonionic detergent containing a high activity for clinical use in the light of Meyer's disclosure.

17. Claims 1, 2, 3, 5, 7, 8, 9, 10 and 12 are rejected under 35 U.S.C. § 102(e) as being anticipated by Kosow et al. (Kosow). Kosow teaches a solution with Factor VIII:C activity containing an amino acid. He elutes the Factor VIII complex containing supernatant from a heparin-coupled chromatographic column, concentrates it by ultrafiltration and adds a histidine buffer and a glycine stabilizer to the ultrafiltered Factor VIII:C solution to provide histidine at a concentration of about

use (page 146, column 1, last 3 lines).

Mathews discloses a process for purifying a protein that has Factor VIII activity by column chromatography. Although the final product is not Factor VIII:C, it can be obtained by eliminating the use of calcium ions in the buffer so the non-covalent bonds between the Factor VIII and von Willebrand factor (Factor C) are not broken (column 7 and 8). The inventors found that exposure of proteins to hydration additives causes the apparent ionic interaction of the protein to increase and the apparent hydrophobic action to decrease. Hydration additives include various sugars, polyhydric alcohols, amino acids and salts (column 5, lines 6-28). Suitable sugars include sucrose, maltose and lactose ,i.e. organic polymers, carbohydrates, while suitable amino acids include glycine (column 15, lines 7-31). Mathew's AHF was purified from human plasma. She uses anion exchange chromatography and uses a physiologically acceptable detergent such as Polysorbate 80 to enhance the desorption of the protein from the column (claims 5-17). Since the final product of column chromatography is eluted from the column, her final product is a solution. Although she does not teach its final composition as a pharmaceutical, she does disclose that the primary use of Factor VIII is intravenous administration to hemophiliac patients (column 1, lines 32-33).

Rasmussen teaches a process for production of Factor VIII by precipitation of an aqueous solution of cryoprecipitate from

blood plasma using polyethylene glycol (PEG) and a salting-in agent, such as an amino acid. The amino acids may include basic amino acids such as lysine, arginine, and histidine as well as polar amino acids such as glutamine and glycine (column 3, lines 40-48). It would have been obvious to one of ordinary skill in the art at the time of the invention to stabilize Factor VIII:C containing solutions with amino acids and one of its salts and/or a detergent or organic polymer. One would have been motivated to use Meyer's preparation of Factor:C concentrate using Mathew's process of column chromatography and utilizing the stabilizing agents taught by Rasmussen. The expected result of a stabilized Factor VIII:C protein is prima facie obvious. Applicants' invention is, therefore, rendered obvious.

Any inquiry concerning this communication should be directed to P. Lynn Touzeau, Ph.D at telephone number (703) 308-0196.

PLT 10 December 1992

JEFFREY E. RUSSEL
PRIMARY PATENT EXAMINER
ART UNIT ~~113~~ 1815